

The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals Regarding the Clinical Staging of Small Cell Lung Cancer in the Forthcoming (Seventh) Edition of the Tumor, Node, Metastasis Classification for Lung Cancer

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on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions

Background: Small cell lung cancer (SCLC) is usually classified using the limited and extensive definition. The tumor, node, metastasis (TNM) classification should also be applicable to SCLC, but it has only been reported in small surgical series. The current analysis looks to the impact of the TNM system on the clinical staging of SCLC and of the new International Association for the study of Lung Cancer (IASLC) proposals.

Methods: Using the IASLC database, survival analyses were performed for clinically staged patients. Prognostic groups were compared, and the new IASLC TNM proposals were applied to this population and to the Surveillance, Epidemiology, and End Results (SEER) database.

Results: The IASLC database contained 12,620 eligible cases of small cell histology. TNM staging was available for 8088 patients. Survival was directly correlated to both T and N category. Differ-

ences were more pronounced in patients without mediastinal or supraclavicular nodal involvement. Stage grouping using the sixth edition of TNM also differentiates survival except between IA and IB. Patients with pleural effusion regardless of the cytology have an intermediate prognosis between limited and extensive disease. The IASLC proposals for the seventh edition of the TNM classification also apply to this series of SCLC and to the SEER database.

Conclusion: TNM staging is recommended for SCLC, and stratification by stage I-III should be incorporated in clinical trials of early-stage disease. Further studies are needed to clarify the impact of pleural effusion and the extent of N3 disease.

Key Words: Small cell lung cancer, Staging.

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Lung cancer is the leading cause of cancer-related mortality in the western world, with recent statistics showing that it accounts for more than 1,000,000 deaths each year globally.¹ Small cell lung cancer (SCLC) represents only 15% to 20% of lung cancers overall, with incidence rates declining among men but continuing to increase among women in most countries.² It is distinguished by its rapid growth rate, early dissemination to regional lymph nodes and distant sites, and its sensitivity to chemotherapy and radiotherapy.³ The introduction of chemotherapy to the treatment of SCLC led to significant improvements in median and 5-year survival rates in the 1970s through 1990s,⁴ but recently survival seems to have reached a plateau for both localized and advanced SCLC.

Staging of lung cancer is second in importance only to the pathologic determination of cell type. Accurate staging provides prognostic information, and stage determines treatment strategies for all types of lung cancer. The first staging system for SCLC was introduced in the 1950s by the Veterans' Administration Lung Study Group (VALSG) for use in

their randomized clinical trials.⁵ This simple system divided SCLC into two disease subgroups termed “limited” and “extensive” disease. Limited disease (LD) was characterized by tumors confined to one hemithorax, although local extension and ipsilateral, supraclavicular nodes could also be present if they could be encompassed in the same radiation portal as the primary tumor. No extrathoracic metastases could be present. All other disease was classified as extensive disease (ED).

In 1989, the International Association for the Study of Lung Cancer (IASLC) issued a consensus report⁶ that, for the first time in 30 years, introduced changes to the VALSG staging system. This report suggested that LD should be expanded to include tumors limited to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal and ipsilateral and contralateral supraclavicular nodes. They also recommended that patients with ipsilateral pleural effusion, regardless of whether cytology is positive or negative, be considered to have LD if no extrathoracic metastases were detected.

The tumor, node, metastasis (TNM) staging systems of the American Joint Committee on Cancer Staging (AJCC)⁷ and the Union Internationale Contre le Cancer (UICC)⁸ are also applicable to SCLC, but they are used less frequently in clinical practice because these two staging systems have historically relied on surgical confirmation for their accuracy, and patients with SCLC seldom present at a stage for which surgery is appropriate. However, in small surgical series of patients with SCLC, the TNM staging system has been shown to be prognostic of outcome.^{9–21} TNM staging in non-surgical series is rarely reported.^{22,23}

The IASLC has established a database containing staging and a minimum of 5-year survival data for more than 100,000 patients with lung cancer from around the world, presenting between 1990 and the end of 2000. Among these are more than 12,000 patients with SCLC. This database was established to assess the current stage categories as defined by the AJCC⁷ and the UICC sixth edition,⁸ with the goal of redefining and regrouping of T and N descriptors, to make recommendations for change if and where appropriate. These analyses were performed initially on the large 67,725 case non-small cell lung cancer (NSCLC) database,^{24–27} then applied to the smaller SCLC cohort. Proposed changes for the UICC seventh edition for NSCLC that are relevant for SCLC are mainly those that result in changes to T staging. It has been recommended that large sized tumors (>7 cm) become T3; additional nodules within the same lobe as the primary tumor also become T3; ipsilateral intrapulmonary nodules in other lobes become T4; and all pleural effusions regardless of cytology become M1. It is also recommended that pleural effusions in the absence of other metastatic sites be designated M1a, with M1b reserved for all other metastatic involvement.^{24,26}

We herein report our analysis of clinical TNM staging for SCLC using the current sixth edition TNM staging system for lung cancer and compare this with the proposed new groupings as defined by the IASLC analyses in NSCLC. We focus on the clinical staging of SCLC because fewer than 5% of patients are eligible for pathologic surgical staging.

METHODS

Statistical Analysis

The database on which these analyses are based was created by the IASLC to inform revisions for the seventh edition of the UICC *TNM Classification of Malignant Tumors* staging manual in lung cancer due to be published early in 2009. To be eligible for inclusion in the IASLC database, patients were required to have a new diagnosis of either SCLC or NSCLC, an initial presentation from 1990 to the end of 2000, adequate staging information at baseline, and adequate follow-up for survival.

There were no minimal staging requirements for inclusion in the database, and details of staging were not recorded.

TNM stage groupings for NSCLC were developed based on recommendations made by the individual T, N, and M subcommittees for changes to their respective components. Using these modified categories, a small number of candidate stage grouping schemes were developed, initially using a recursive partitioning and amalgamation algorithm.²⁸ The analysis grouped patients based on best stage (pathological if available, otherwise clinical) after determination of best-split points based on overall survival on indicator variables for the newly proposed T/M category and an ordered variable for N category. This analysis was performed on a randomly selected training set comprising two thirds of the available data that met the requirements for conversion to the newly proposed TNM categories ($n = 17,726$), reserving 9133 cases for later validation. The random selection process was stratified by type of database submission and time of case entry (1990–1995 vs 1995–2000).²⁹ Selection of a final stage grouping proposal from among the candidate schemes was based on its statistical properties in the training set and its relevance to clinical practice and was arrived at by consensus.

Analyses focusing on sixth edition TNM were applied to the subset of SCLC cases for which complete clinical TNM stage was provided. The newly proposed TNM stage groupings were applied to the set of SCLC cases that had sufficient descriptors to reclassify according to the new TNM stage scheme. Analyses focusing on pleural effusion required only a designation of limited or extensive stage disease by the VALSG system (or adequate TNM staging to derive this determination) and sufficient information to determine presence/absence of pleural effusion.

Survival was measured from the date of entry (date of diagnosis for registries and the date of registration for protocols) and was estimated by the Kaplan-Meier method. Prognostic groups were compared formally by Cox proportional hazards regression analysis, using the SAS System for Windows Version 9.0 PHREG procedure.

RESULTS

Population

Of the 100,869 patients with information submitted to the IASLC database, 81,015 met the initial screening requirements of having a new diagnosis rather than recurrent diagnosis of either SCLC or NSCLC, presentation from 1990 to the end of 2000, adequate follow-up for survival, and adequate staging information at baseline. From the 13,290 SCLC

cases meeting the initial screen, 670 with mixed histology or with conflicts between TNM and extent of disease were excluded, to yield 12,620 eligible cases of small cell histology. Of the 12,620 eligible SCLC cases, 4532 had LD or ED classification only (Table 1). TNM staging was available for 8088 patients: 3430 cM0 cases had full clinical TNM data, 343 had full pathologic TNM staging, and 4530 were classified as cM1 (clinical metastatic disease). The 12,620 cases originated from four global regions: Europe (56%), North America (35%), Asia (3%), and Australia (6%). Of the cases, 52% were from clinical trials, 43% from population-based registries or single-institution series or registries, and the rest from consortia. For cases with complete clinical TNM staging, the proportions were: clinical trials 32%, population-based registries or single-institution series or registries 60%, and consortia 8% (Table 2). Because most patients with SCLC are staged only clinically, we focus on the clinical staging of this malignancy in this article; the surgical series will be reported separately. A complete listing of data contributors is given in Appendix A.

T Category

As shown in Figure 1A, increasing clinical T category, using the sixth edition TNM staging system was associated with progressively lower survival in patients who did not have evidence of metastatic (M1) involvement. Comparisons between T categories and 1- and 5-year survival rates are shown in Table 3. Patients with clinical T1 had significantly better survival than those with T categories 2–4. A comparison of clinical category T1 versus T2 yields a hazard ratio (HR) of 1.48 ($p < 0.0001$), and the trend continues with significant differences between T2 versus T3 and T3 versus T4 (see Table 3). The p value for the ordered log rank test (a test against ordered alternatives for survival data) is less than 0.0001.^{28,29}

N Category

As shown in Figure 1B and Table 4, increasing clinical N category was associated with progressively lower survival. Patients with clinical N0 or N1 tumors had significantly better survival than did those with N2 or N3 tumors. The difference between cN0 and cN1 is not significant (HR 1.02, $p = 0.76$). The cN2 and cN3, although significantly different, have similar median survivals (14 vs. 12 months, HR 1.18). The

difference between the N1 and N2 is the largest (median 19 vs. 14 months, HR 1.40, $p = 0.0001$) and represents the primary separation for clinical N category. The p value for the ordered log rank test is less than 0.0001.

Survival for clinical T categories within the four clinical N categories 0–3 is shown in Figure 2. Although increasing T category seems to be associated with worse survival in each N category, the differences seem to be clinically meaningful only for patients without mediastinal or supraclavicular nodal involvement.

Survival According to TNM Stage

Survival by clinical TNM stage sixth edition is shown in Figure 1C. The near superimposition of stage IA together with IIA, and stage IB with IIB, are most likely a reflection of the separation between the T1 cases (comprising IA and IIA) and the T2 and T3 (IB and IIB). Pair-wise comparisons between adjacent stage groupings are shown in Table 5. All differences are significant, but for the reason just discussed, the hazard ratio for IIA versus IB is the reverse of what would be expected.

Pleural Effusion

In the proposals from the IASLC for the forthcoming (seventh) edition of the TNM classification for lung cancer, the presence of a pleural effusion in patients with NSCLC will now be considered as M1 disease. In the SCLC database, information concerning the presence or absence of pleural effusion or other distant sites was available for 1258 patients with otherwise limited disease (1113 of whom were without pleural effusion, 145 with pleural effusion) and 4500 patients with ED with other metastatic sites. Of the 145 cases of LD with pleural effusion, 81 were actually designated as ED without any other metastatic sites. These 81 were assumed to have LD with pleural effusion. Surgically managed cases were excluded. As can be seen from Figure 3A, the survival of patients with LD with effusion is intermediate between those of patients with LD without effusion and patients with ED (ordered log rank p value <0.0001).

The result of cytologic examination of the pleural effusion was available for only 68 patients in the database. As shown in Figure 3B, the survival of patients with LD with effusion, whether cytologically negative or positive, remained intermediate between those of patients with LD

TABLE 1. Summary of 12,620 Small Cell Lung Cancer Cases from the IASLC International Staging Project Database

VALSG/IASLC Stage	Available TNM staging					Total
	Clinical TNM	Pathological TNM	Clinical and Pathological TNM	cM1	Extensive or Limited Only	
Not classified	1819	127	193	1532	0	3671
Extensive	88	0	4	2998	2038	5128
Limited	1308	1	18	0	2494	3821
Total	3215	128	215	4530	4532	12620

VALSG, Veterans' Administration Lung Study Group; IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, metastasis.

TABLE 2. Sources of Small Cell Lung Cancer Cases with Complete TNM Stage

Type of Database	Available TNM Staging				Total
	Clinical TNM	Pathological TNM	Clinical and Pathological TNM	cM1	
Registry	634	6	9	1720	2369
Surgical series	31	67	3	5	106
Clinical trial	1027	0	1	1556	2584
Series	742	2	31	596	1371
Consortium	240	11	171	263	685
Institutional registry	541	0	0	390	931
Surgical registry	0	42	0	0	42
Total	3215	128	215	4530	8088

TNM, tumor, node, metastasis.

without effusion and patients with ED, and the survival of patients with LD with positive effusions was superior to that of patients with ED (ordered log rank p value <0.0001).

Proposals from the IASLC for Stage Groupings in the Seventh Edition of the TNM Classification for Lung Cancer

It was not possible to classify all SCLC cases according to the proposed IASLC stage groupings because details for the T descriptor frequently was inadequate, particularly with respect to size, presence of additional intrapulmonary nodules, and involvement of the pleura. Figure 4A shows survival according to the TNM stage sixth edition for the smaller cohort of patients ($n = 2464$) with full T descriptor data. With the exception of the extremely small subgroup of eight patients with stage IIA, it can be seen that increasing stage is associated with progressively shorter survival. Figure 4B shows the survival of the same cohort of patients using the IASLC stage groupings proposed for the UICC seventh edition, and Figure 4C shows the proposed IASLC groupings applied to the much larger Surveillance, Epidemiology and End Results (SEER) data base of the National Cancer Institute. In the SEER database, for patients registered with an initial diagnosis of SCLC during the years 1998 through 2000 inclusive, the proposed IASLC system works well with increasing stage being associated with decreasing survival.

DISCUSSION

At the time of initial diagnosis, approximately two thirds of patients with SCLC have clinical evidence of hematogenous metastases (M1); for the remaining one-third, most patients have clinical evidence of extensive nodal involvement in the hilar, mediastinal, and sometimes even the supraclavicular regions. For that reason, surgical resection is seldom offered; instead, patients are treated with systemic chemotherapy with or without radiation. Although TNM staging has been applied in small series of patients with SCLC treated either with surgery alone or with combined modality therapy including surgery,⁹⁻²¹ a simpler staging system assigning patients to either LD or ED is used most frequently in clinical practice.^{5,6} Patients with LD cancers (confined to the thorax) are treated with chemotherapy and

thoracic radiation, whereas, for the most part, patients with ED (distant hematogenous metastases) receive only chemotherapy.

In general, it has been believed that more precise staging of SCLC using the TNM system does not provide extra guidance with respect to selection of treatment modality because so few patients are eligible for surgery. However, a more precise definition of nodal involvement may be of particular relevance for radiation treatment. The simple designation of LD does not provide adequate information for accurate radiotherapy planning because it does not differentiate between the presence or absence of ipsilateral and contralateral supraclavicular nodes, and ipsilateral and contralateral hilar or mediastinal nodes. According to the 1989 IASLC staging system for SCLC, all of these nodal stations are included in LD. In the modern era of conformal techniques and increasing radiation dose for SCLC, it is likely no longer appropriate to treat all patients with LD in the same way, and radiation fields must be determined using more precise nodal categories.

The SCLC subgroup of patients in the IASLC staging initiative represents the largest cohort of patients with this malignancy ever to be reported. In particular, it is the largest cohort of patients with SCLC to have been staged using the TNM system apart from small surgical series, most of which had fewer than 50 patients.⁹⁻²¹ These surgical series clearly showed that TNM staging could identify patients with different prognoses.

The more important question, however, is whether the old VALSG and IASLC staging classifications should be abandoned and whether clinical TNM staging, as used for NSCLC, should be applied to SCLC as proposed by the UICC. In our large clinically staged series, patients with clinical T1 disease had significantly better survival than those with T2 disease (HR 1.48, $p < 0.0001$) and all other T categories, although they represented only 13.7% of all patients. However, the test for trend among the four T groupings was highly significant. In a pattern of care study performed in Japan including only patients with limited disease, the T category was also a significant prognostic factor for survival in a multivariate analysis.¹⁸

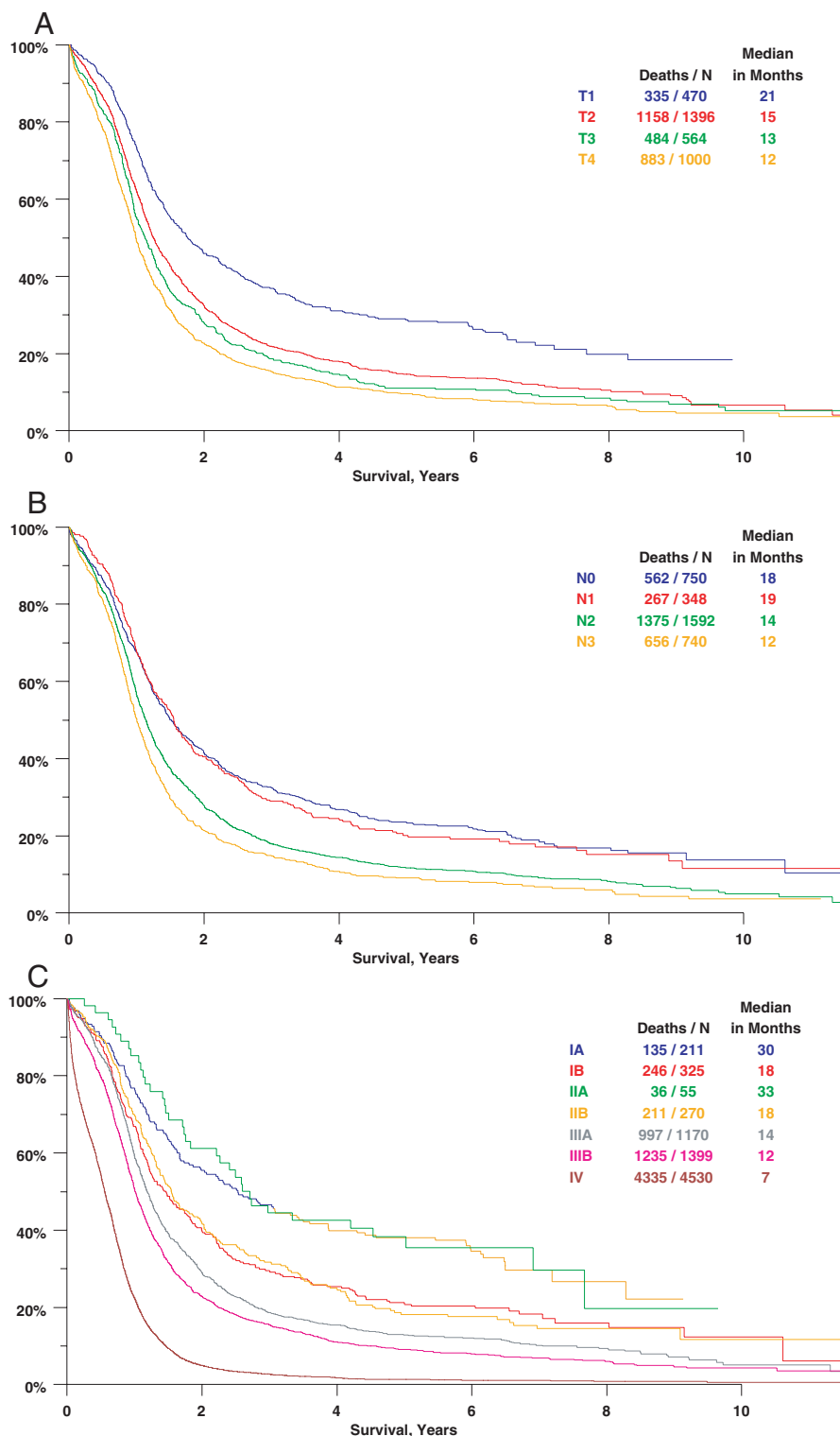


FIGURE 1. Survival by (A) clinical T Category, (B) clinical N Category, and (C) clinical TNM category (sixth edition of TNM).

With respect to N category, patients with clinical N0 or N1 tumors had significantly better survival than those with N2 or N3 tumors, although the difference between N0 and N1 was not significant, and the greatest difference in survival was seen between N1 and N2. It is likely that the patients

with T1-2,N0-1,M0 tumors (i.e., stage IA, IB, IIA and IIB [N0 and N1]) are the same as those previously classified by the University of Toronto Lung Group as “very limited.”²²

Unfortunately, the database did not contain enough information to determine whether the survival of patients

TABLE 3. Overall Survival Comparisons for Clinical Category T1 to T4 (any N) M0 Small Cell Lung Cancer, IASLC Data

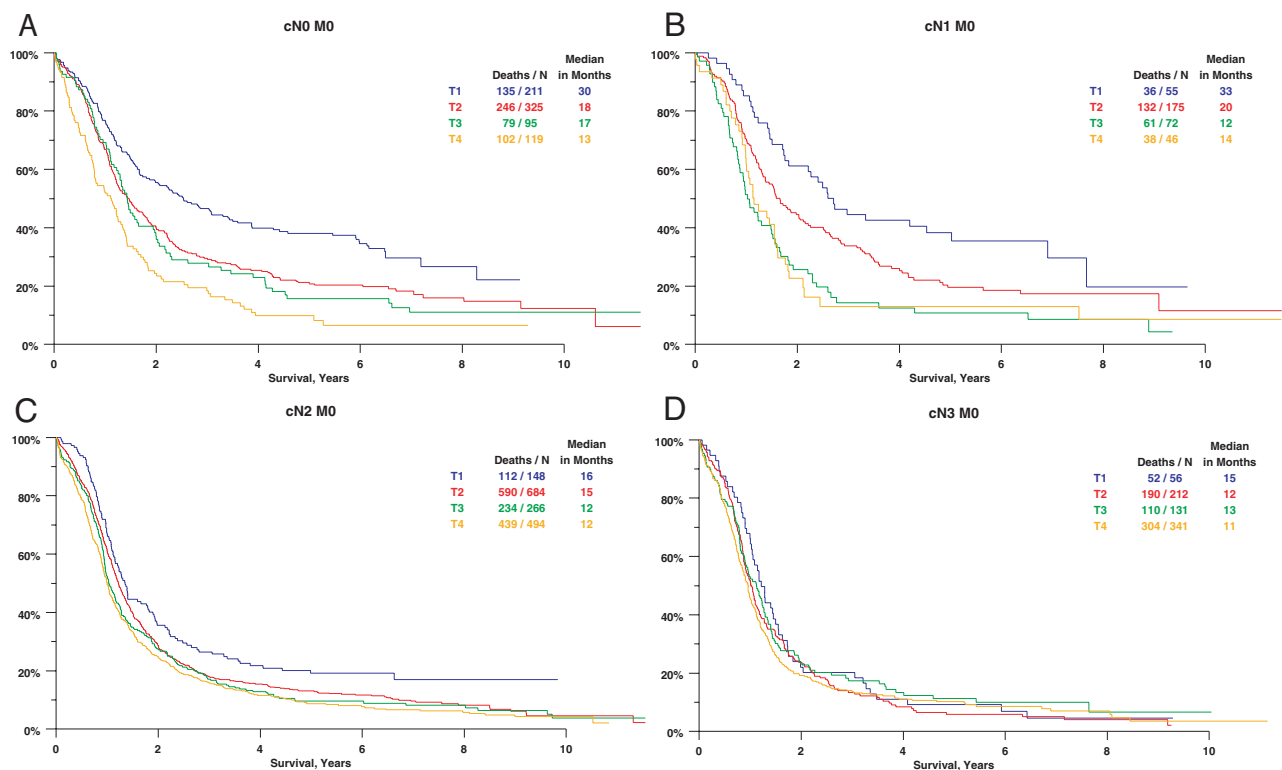
T Category	n	1-yr Survival (%)	5-yr Survival (%)	Comparison	HR	p
T1	470	73	29			
T2	1396	62	15	T2 vs. T1	1.48	<0.0001
T3	564	55	11	T3 vs. T2	1.14	0.0185
T4	1000	49	10	T4 vs. T3	1.17	0.0055

HR, hazard ratio.

TABLE 4. Overall Survival Comparisons for Clinical Category N0–N3 (any T) M0 Small Cell Lung Cancer, IASLC Database

N Category	n	1-yr Survival (%)	5-yr Survival (%)	Comparison	HR	p
N0	750	68	24			
N1	348	68	20	N1 vs. N0	1.02	0.7552
N2	1592	56	12	N2 vs. N1	1.40	<0.0001
N3	740	50	9	N3 vs. N2	1.18	0.0006

HR, hazard ratio.

**FIGURE 2.** Survival by clinical T category, within clinical N categories.

with N3 contralateral mediastinal nodes differed from that of patients with N3 supraclavicular nodes, and it could not address differences in outcome for ipsilateral versus contralateral supraclavicular nodal involvement. In the IASLC staging system,⁶ both ipsilateral and contralateral supracla-

vicular nodes are included in LD. Therefore, more precise nodal categories should be recorded in future validation studies that will have prospectively collected data.

In the past, the traditional radiotherapy ports for chest irradiation for SCLC were large and sometimes included

TABLE 5. Overall Survival Comparisons for Clinical TNM Stage Category Small Cell Lung Cancer, IASLC Database

Stage	N	1-yr Survival (%)	5-yr Survival (%)	Comparison	HR	p
IA	211	77	38			
IB	325	67	21	IB vs. IA	1.48	0.0003
IIA	55	85	38	IIA vs. IB	0.62	0.0075
IIB	270	70	18	IIB vs. IIA	1.57	0.0118
IIIA	1170	59	13	IIIA vs. IIB	1.32	0.0003
IIIB	1399	50	9	IIIB vs. IIIA	1.21	<0.0001
IV	4530	22	1	IV vs. IIIB	2.16	<0.0001

HR, hazard ratio.

“prophylactic” treatment of areas such as the contralateral hilum and both supraclavicular fossae. In essence, therefore, treatment frequently paralleled the IASLC definition of limited disease. However, only moderate dose radiation could be delivered to such large volumes. The inability to deliver high doses to these large volumes may, in part, explain the high rates of failure at the primary site reported in most studies

despite the administration of thoracic radiotherapy. Several recent trends make more precise nodal staging critical for SCLC. As is the case in NSCLC, reduction of the radiotherapy field size to cover only the known area of macroscopic disease is being recommended for SCLC. Also, the high local failure rate despite the addition of radiation to chemotherapy is leading to the investigation of higher radiation doses or

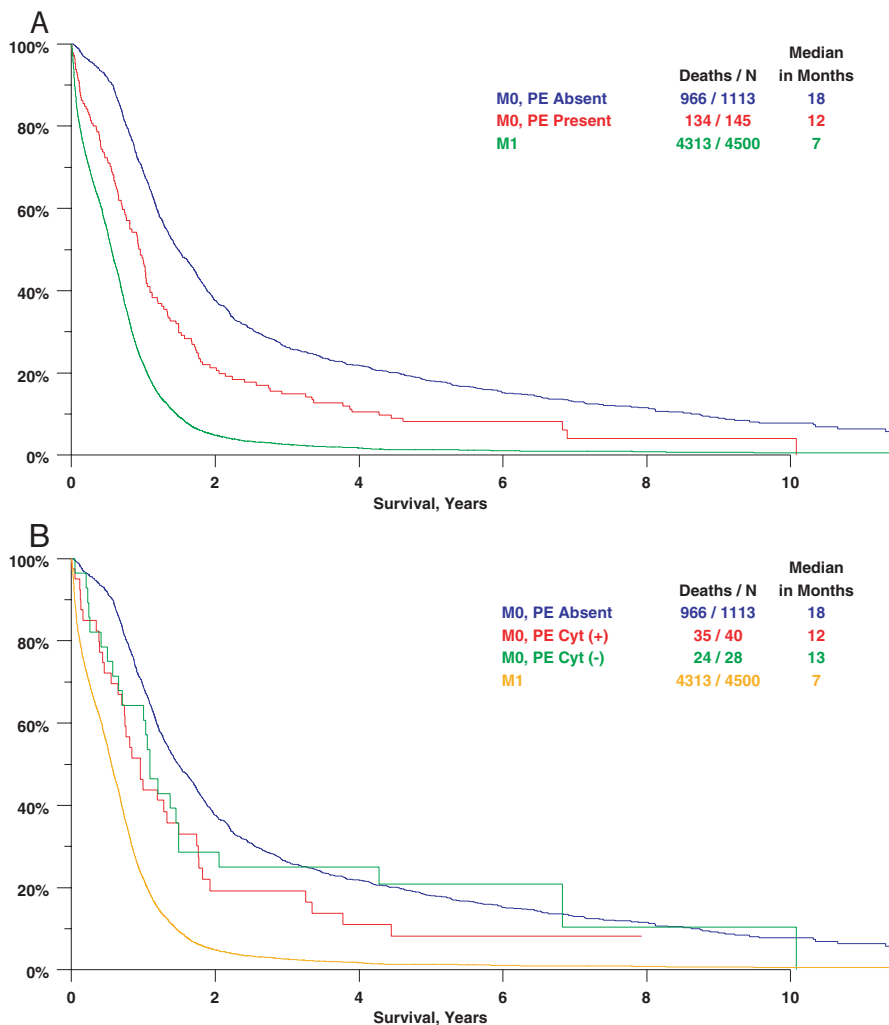


FIGURE 3. Survival by pleural effusion status (surgical cases excluded). *A*, All pleural effusions included. *B*, Only effusions with cytologic evaluation comparing cytology-positive with cytology-negative effusion.

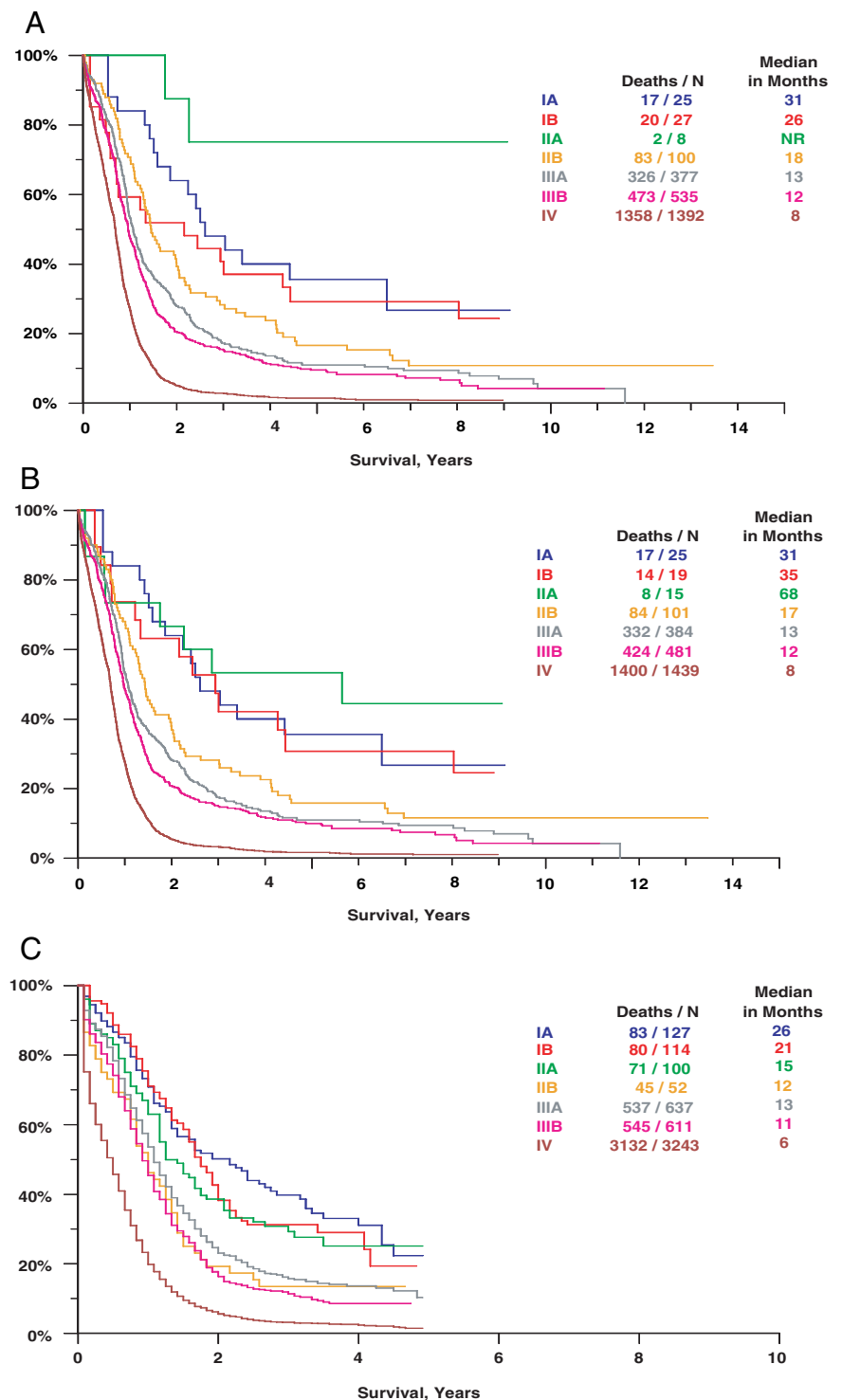


FIGURE 4. Survival by (A) clinical sixth edition of TNM, including only those cases with sufficient information to derive IASLC proposed TNM stage; (B) IASLC proposed TNM stage; (C) survival by IASLC proposed TNM stage in the Surveillance, Epidemiology and End Results database.

more aggressive combined radio-chemotherapy regimens.^{30–32} To avoid toxicity from large volume fields, it will be essential to identify the most appropriate patients for such therapy, and more precise staging will be key to the ability to do this. It will also be very important to examine the patient populations in reports of clinical trials of altered fractionation and high-dose radiation (particularly single-arm phase I or II studies)

because all patients with LD as defined by the IASLC may not be included in those studies, and this may have an effect on the survival outcomes. For example, in the landmark Turrisi trial, patients with pleural effusions, regardless of the cytology, and those with contralateral hilar or supraclavicular adenopathy were excluded.³⁰ In this analysis, the survival of patients with IIIA and IIIB disease seems to be less than that

reported in recent trials of high-dose radiation, hyperfractionated radiation, or concurrent chemotherapy and radiation therapy in LD SCLC. This may, in part, be because of less aggressive treatment practices in some parts of the globe where concurrent chemotherapy and radiation is seldom administered and where high-dose or hyperfractionated radiation is not considered standard. Alternatively, however, these survival rates may be a more accurate reflection of the true outcome of LD SCLC than those reported from clinical trials in which trial patients are a highly selected subgroup of LD overall.

If the proposals made by the IASLC for the forthcoming (seventh) edition of the TNM classification for lung cancer are accepted by the UICC and the AJCC, patients with pleural effusion will, in the future, be classified as having M1 (or extensive) disease. Our analysis shows that patients who have pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between that of stage I–III without effusion and stage IV. A similar observation was reported by Perng et al. in a series of patients treated in Taiwan.²³ Therefore, we recommend that pleural effusion should be a stratification parameter in clinical trials for both LD and ED SCLC. Having even a small proportion of patients with pleural effusion in LD trials could affect outcome significantly if they are not balanced between the arms, as could patients with only a pleural effusion in ED trials. Unfortunately, we did not have enough patients in our analysis to make a clear statement concerning cytology-positive or -negative effusions. Similarly, no information was available with respect to the presence of a pericardial effusion. This information must be collected prospectively in future studies.

It seems that TNM staging can identify subgroups of patients with distinct prognoses from within the broad definition of LD. However, the question still remains as to the value of applying the TNM system of staging to all patients with LD SCLC. Exact TNM stage is unlikely to alter treatment decisions for most patients with LD because combined modality therapy will be offered to patients with good performance status in most subsets of stage I, II, or III. The only potential exception to this might be the subgroup of patients with N3 supraclavicular nodal involvement, whether unilateral or bilateral. Whether to include supraclavicular nodes in the radiation treatments field remains an unresolved issue and is one that will require careful documentation for future prospective database analyses.

Our analysis suggests that, in the context of clinical trials in LD, accurate TNM staging may be critical and suggests that stratification based on TNM stage may be important. Survivals for clinical stages I and II are significantly different from those of stage III with N2 or N3 involvement. Therefore, the SCLC staging subcommittee of the IASLC Lung Cancer Staging Project recommends that TNM staging should be applied to SCLC and that stratification for stage should be incorporated into all trials in LD SCLC, particularly those addressing thoracic and prophylactic cranial radiation questions and those that include a surgical treatment arm. The small survival differences that are

expected in these trials could be affected significantly by imbalances in the two patient subgroups of stage I/II versus III. For tumor registries, the clinical and, where possible, pathologic TNM designations should be recorded. It will always be possible to derive the LD and ED subsets from these data.

In summary, the proposals made by the IASLC for the forthcoming (seventh) edition of the TNM staging system seem to have relevance to SCLC. The SCLC subcommittee of the IASLC Lung Cancer Staging Committee therefore recommends that TNM staging be applied in SCLC and that stratification by TNM stage be incorporated into clinical trials in stage I–III SCLC. For prospective staging validation studies, more information must be collected to define the N category more clearly and to determine whether there is a difference in prognosis for patients with cytology-negative or -positive pleural effusions and for patients with pericardial effusions. In addition, in future studies, data concerning other prognostic variables, such as gender and performance status, and more detailed staging data should also be collected for multivariate analysis to isolate the effect of stage in this malignancy.

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APPENDIX 1

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